Challenges in Management of Rare Chronic Diseases

Pramod K. Mistry, MD, PhD, FRCP (London), FAASLD, MA, Yale Privitim.
Professor of Medicine, Pediatrics and Molecular & Cellular Physiology
Director of National Gaucher Disease Center.

Rare Diseases COPAC Summit, 2022

MAT-CO-2202551 08/2022

Yale SCHOOL OF MEDICINE

Disclosures

- Employee of Yale University, Professor

- I have received research funding from
  NIH, NIDDK K24, NIDDK/ R01 NIAMS AR 065932
  Gaucher Generation Program Senior Investigator Award
  National Gaucher Foundation
  Sanofi Genzyme

- Chair, Project Hope Gaucher Humanitarian Initiative

- Chairman, International Gaucher Registry, North American, ICGG

- Board Member, India Charitable Access Program, INCAP

- I have received travel support from Sanofi Genzyme

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Synopsis

- General challenges in rare, chronic diseases
  - Heterogeneous phenotypes
  - Variable natural history
  - Single centers have only few patients
  - Variable monitoring
  - Incomplete capturing of outcomes data
- Gaucher disease in particular
  - Pivotal clinical trials capture outcomes in narrowly defined disease spectrum
  - Variable disease spectrum and natural history in individual geographies
  - Disease Registries
  - Assessing therapeutic options
  - Need for national collaborative groups

Efficacy Data for Macrophage-Targeted ERT

- First-generation ERT since 1991
  - Alglucerase and imiglucerase
    - Made ERT the standard of care for GD
    - More than 5,000 patients treated globally, and data captured in ICGG registry
    - 10-year data showed reversal of hepatosplenomegaly, cytopenia, bone crises, and osteopenia and reduction in bone pain and improvement of QOL
    - Cumulative 54,000 patient years of experience
- New ERT agents since 2011
  - Velaglucerase (human fibrosarcoma cell-derived)
  - Taliglucerase (plant cell-derived)
    - Reversal of organomegaly and cytopenia
    - Limited bone data

Rosenbloom BE, et al. *Crit Rev Oncog*. 2013;18:163-75; Bennett LL, et al. *Ann Pharmacother*. 2013;47:1182-93; Ortolando S, et al. *Recent Pat Endocr Metab Immune Drug Discov*. 2014;8:9-25; Weinreb NJ, et al. *J Inherit Metab Dis*. 2013;36:543-53; Morris JL. *Clin Ther*. 2012;34:259-71; Hollak CE. *Core Evid*. 2012;7:15-20; Damiano AM, et al. *Qual Life Res.* 1998:7:373-86.

OPINION

The most transformative drugs of the past 25 years: a survey of physicians

Aaron S. Kesselheim and Jerry Avorn

Table 2 | **Top transformative drugs or drug classes identified via modified Delphi protocol**

Clinical field	Consensus top selection*	Consensus second-place selection	Notes on results
Anaesthesiology	Propofol (11)	Remifentanil (2)	Propofol was a clear consensus choice
Cardiology	Lovastatin (7)	ACE inhibitors (0)	Alteplase (recombinant tPA) came in a close third, receiving fewer second-place mentions than ACE inhibitors
Dermatology	TNF blockers (7)	OnabotulinumtoxinA (3)	Participants selected multiple TNF blockers, so the drugs were considered as a single class; some participants mentioned the transformative role of isotretinoin, which fell outside our date range for inclusion
Endocrinology	Bisphosphonates (6)	Metformin (3)	Most participants picked out multiple bisphosphonates, so the individual drugs were collated into a group
Gastroenterology	Omeprazole (6)	TNF blockers	Omeprazole was the runaway choice
Infectious diseases	HIV protease inhibitors (4)	Zidovudine (2)	Participants were inclined to include all of the initial group of HIV protease inhibitors (saquinavir, ritonavir and indinavir)
Genetics	Alglucerase (4)	Nitisinone (1)	Many participants also chose sodium phenylacetate and sodium benzoate but noted that the use of sodium benzoate pre-dated the time period of this study

Major Sources of Clinical Data on ERT in GD1: >54,000 patient-years of imiglucerase experience

- 4 major clinical trials of imiglucerase involving nearly 200 patients


Imiglucerase (Cerezyme®) improves quality of life in patients with skeletal manifestations of Gaucher disease


Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort study


Molecular Genetics and Metabolism

A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1

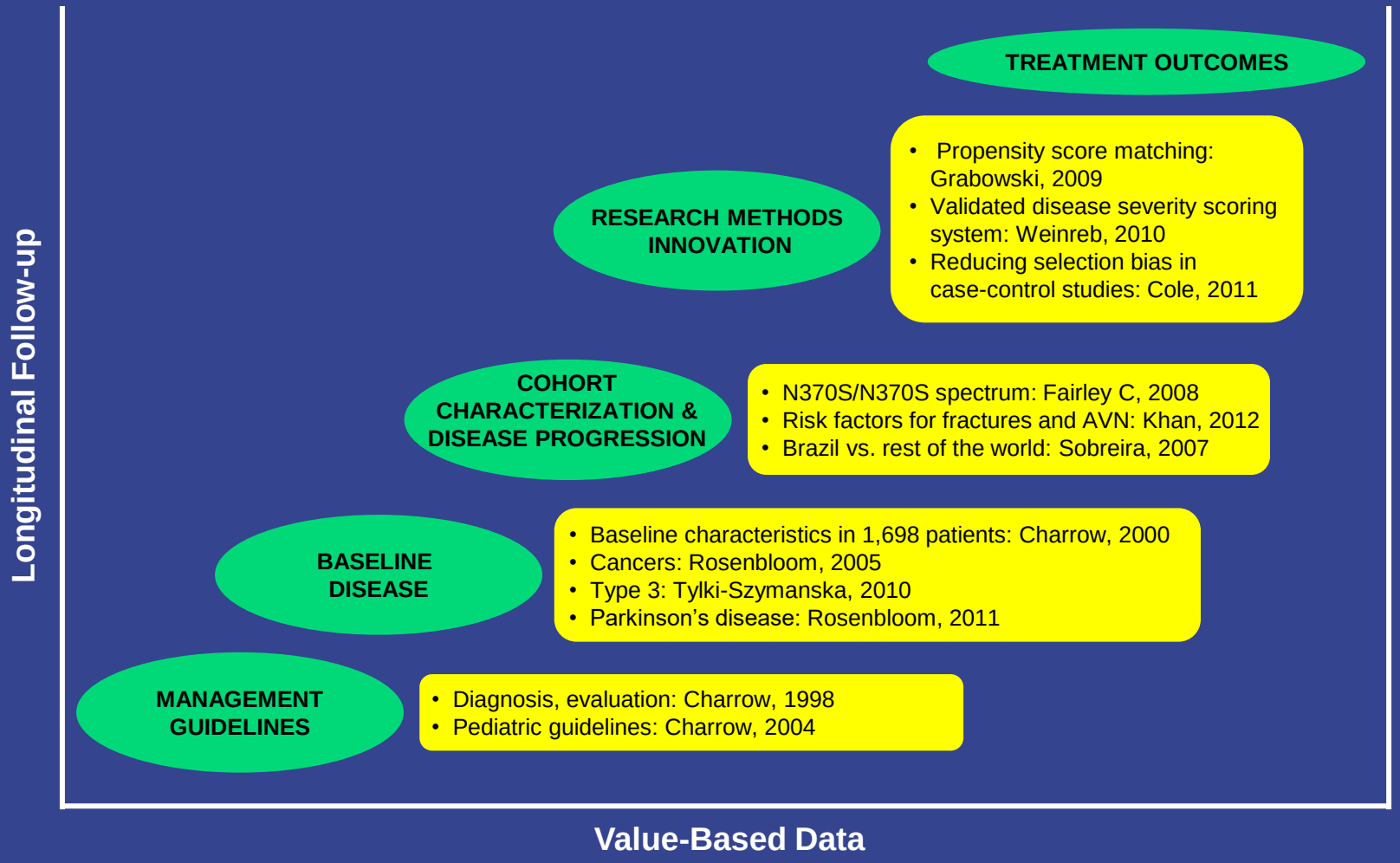
- 31 publications addressing treatment effectiveness from the ICGG Gaucher Registry (currently > 6000 patients enrolled)


Effectiveness of Enzyme Replacement Therapy in 1028 Patients with Type 1 Gaucher Disease after 2 to 5 Years of Treatment: A Report from the Gaucher Registry

The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease

A benchmark analysis of the achievement of therapeutic goals for Type 1 Gaucher disease patients treated with imiglucerase

The GD Registry: A Foundation for Patient-Centered Outcomes and Comparative-Effectiveness Research



National Gaucher Foundation, Inc. www.gaucherdisease.org/ngf-position-statement.php.

The Changing Paradigm in Healthcare: From Evidence-Based Medicine to Value-Based Medicine

- Effect of healthcare reform
  - Therapeutic interventions will be judged by payers and society by metrics of Value-Based Medicine
    - The effect of therapy on patient-centered outcomes, like the incidence of disease complications, QOL, and survival vs. adverse events
  - In the past, therapeutic interventions were judged on the basis of evidence-based medicine
    - The effect on surrogate markers, like serum cholesterol in coronary artery disease or Hb/platelets and liver/spleen volumes in GD
- Patient-centered outcomes data in GD are only available for alglucerase and imiglucerase

Mushlin AI, et al. *N Engl J Med*. 2010;362:e6;
www.gaucherdisease.org/ngf-position-statement.php.

From Evidence-Based to Value-Based Medicine

	EVIDENCE-BASED MEDICINE	VALUE-BASED MEDICINE
ENDPOINT	**Lab or imaging outcomes**	**Clinical event or patient-reported outcomes**
QUESTIONS	❑ ERT reverses organomegaly	❑ Does ERT decrease the incidence of splenectomy?
	❑ ERT reverses cytopenia	❑ Does ERT prevent the need for blood transfusions? ❑ Does ERT reduce the incidence of bleeding complications? ❑ Does ERT reduce the risk of infections?
	❑ ERT reverses marrow infiltration	❑ Does ERT prevent bone crises
	❑ ERT increases bone density	❑ Does ERT decrease the risk of fractures?
	❑ ERT reverses cytopenia and organomegaly in children	❑ Does ERT reverse growth failure?
	❑ ERT reverses immune dysregulation	❑ Does ERT reduce the risk of cancer?

Courtesy of Dr. Mistry.

Mushlin AI, et al. *N Engl J Med*. 2010;362:e6;

Macrophage-Targeted ERTs: Therapeutic Goals

- Aid in the evaluation of individual patient assessment and response to therapy. There are six published therapeutic goals for patients with GD type 1:
  - Anemia: increase hemoglobin levels to ≥ 11 g/dL for women and children and > 12 g/dL for men
  - Thrombocytopenia: increase platelets to prevent spontaneous blee… spl… elet cou… t
  - Hep… al; for tho… years 1 to 2 and by 30% to 40% by years 3 to 5 of treatment
  - Splenomegaly: achieve a spleen volume of 2 to 8 times normal for those on imiglucerase, reduce spleen volume by 30% to 50% within 1 year of treatment and by 50% to 60% by years 2 to 5 of treatment
  - Aspirational goals are to lessen or eliminate bone pain within 1 to 2 years (no evidence in 2004) and prevent bone crises

Surrogate markers of disease—
not patient-centered clinical outcomes.
Do these correlate with bone crises, need for splenectomy, or bleeding complications?

Pastores GM, et al. *Semin Hematol*. 2004;41:4-14.

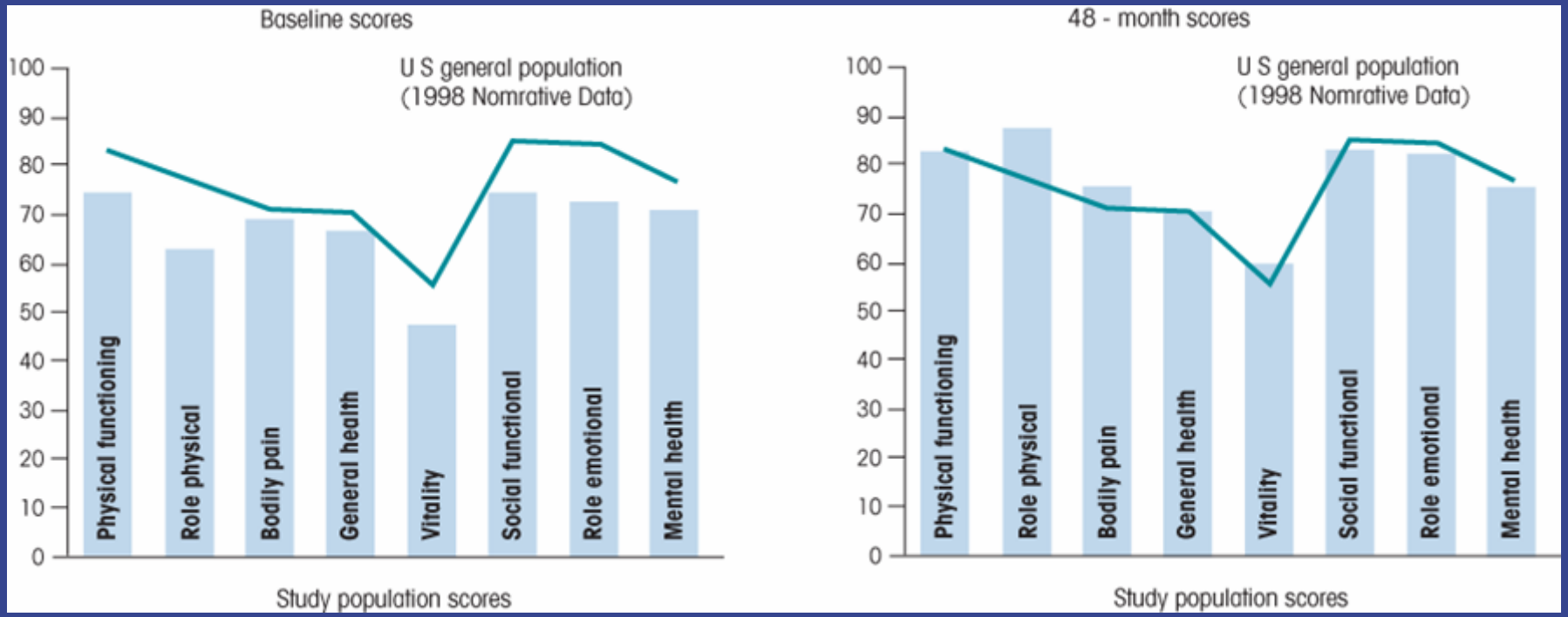
Fostering Value-Based Medicine Through the Registries

14th North American Genzyme LSD Registries Meeting

June 14, 2013
The Westin O'Hare
Chicago, Illinois

Pram Mistry
Lorne Clarke
Daniel Gruskin

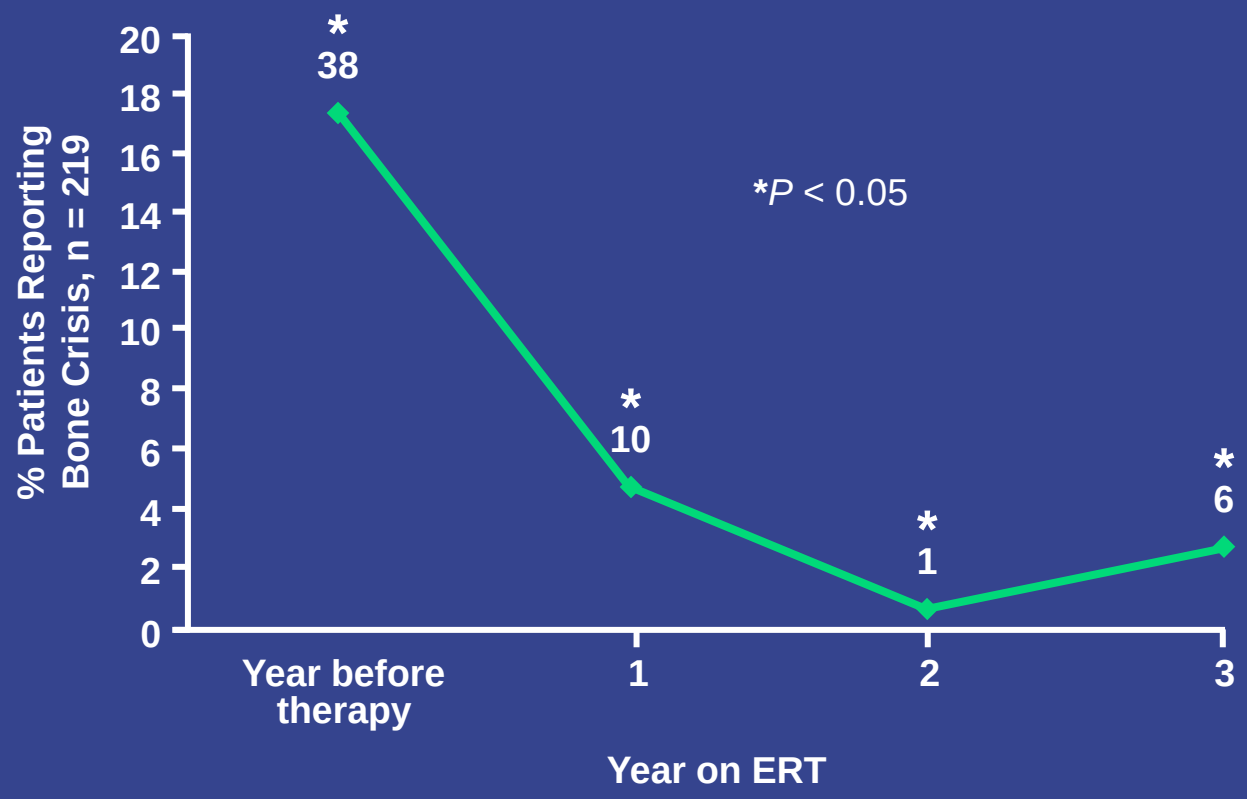
Health-related Quality of Life in GD1 patients with bone disease



Clinically meaningful improvements in SF-36 scores were experienced by Gaucher patients with bone complications who were treated with Cerezyme.

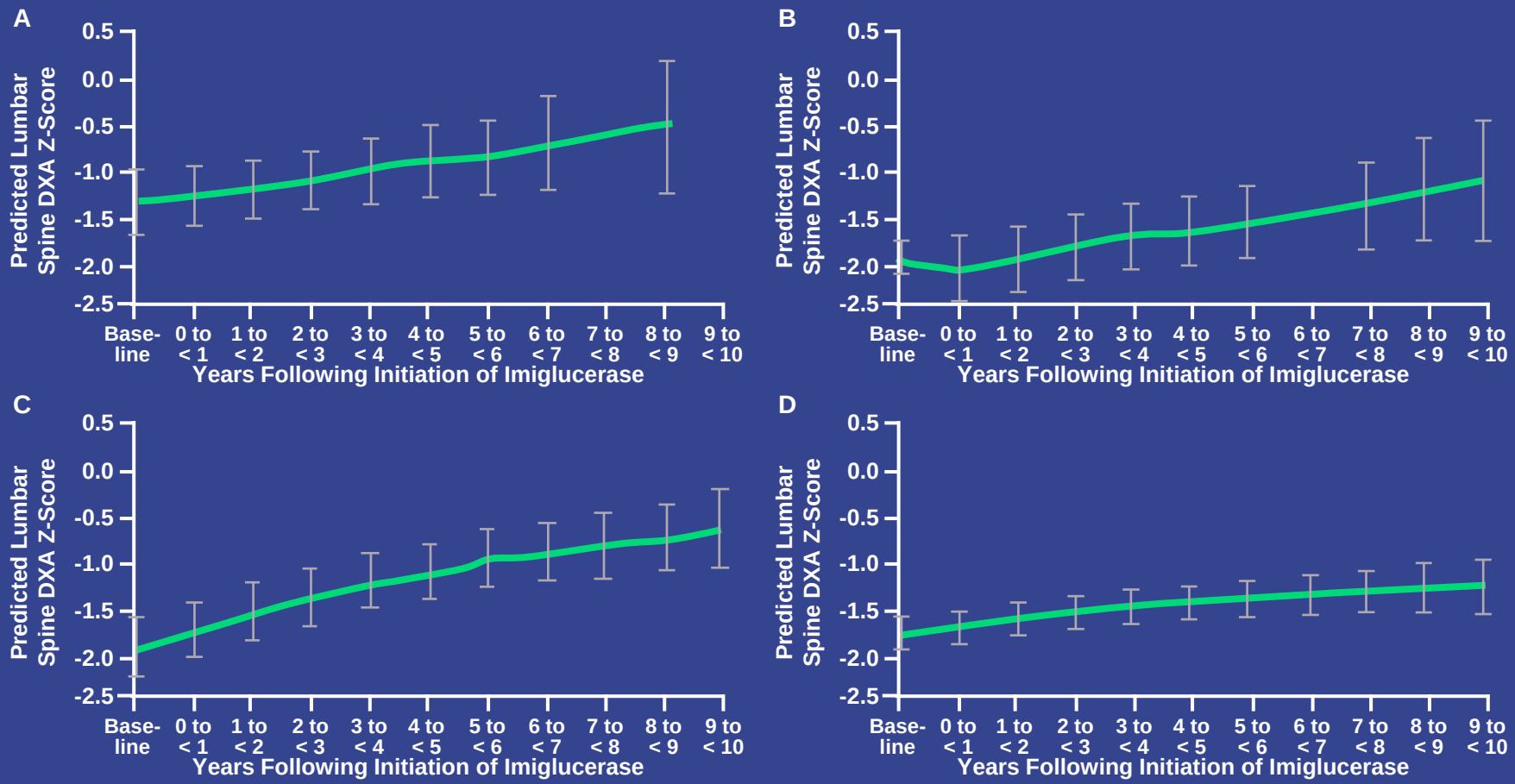
Weinreb N, et al. Clin Genet 2007; 71: 576–588.

Incidence of AVN Is Reduced by Imiglucerase ERT



Charrow J, et al. *Clin Genet.* 2007;71:205-11.

DXA Z-Scores of GD Type 1 Patients With 2 or More Measurements During Imiglucerase Treatment



A. Children (ages ≥ 5 years to < 12 years); B. Adolescents (ages ≥ 12 years to < 20 years); C. Young adults (ages ≥ 20 years to < 30 years); D. Adults (ages ≥ 30 years to ≤ 50 years)

Mistry PK, et al. *Blood Cells Mol Dis*. 2011;46:66-72.

Abcertin: phase 2 of only 5 patients
Phase 3 of only 6 patients

ORIGINAL ARTICLE
Human Genetics & Genomics

JKMS

http://dx.doi.org/10.3346/jkms.2015.30.4.378 • *J Korean Med Sci 2015; 30: 378-384*

A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin® in Patients with Type 1 Gaucher Disease

Table 1. Baseline clinical characteristics of patients with Gaucher disease

No.	Age at diagnosis (yr)	Age at enrollment (yr)	Sex	Height SDS	Weight SDS	Dose of imiglucerase treatment before enrollment (units/kg)	Spleen volume (mL)	Liver volume (mL)	Genotype	Enzyme activity (6-10 nM/hr/mg)
1	20.1	29.9	Male	-0.03	-0.05	30	433	1,518	L444P/D409H	1.07
2	1.4	16.7	Female	0.01	0.15	37.2	596	1,317	L444P/L444P	0.71
3	12.9	18.6	Male	-0.88	0.27	55	297	1,555	G46E/F213I	0.53
4	1.9	8.2	Male	-0.17	-0.2	46	185	898	G46E/F213I	0.95
5	4.5	10	Female	-0.38	-0.92	43	149	647	G46E/R257Q	0.74
Mean ± SD (range)		16.2 ± 8.26		-0.29 ± 0.36	-0.15 ± 0.47	42.24 ± 9.39				

ND, not determined; SD, standard deviation; SDS, standard deviation score.

Korean Med Sci. 2015 Sep;30(9):1373

Erratum: A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin® in Patients with Type 1 Gaucher Disease

Jin-Ho Choi, Beom Hee Lee, Jung Min Ko, Young Bae Sohn, Jin-Sung Lee, Gu-Hwan Kim, Sun Hee Heo, June-Young Park, Yoo-Mi Kim, Ja-Hye Kim, and Han-Wook Yoo

To the Editor:

The authors want to clarify the definition of "biosimilar" based on "Regulatory expectations and risk assessment for biotherapeutic products. World Health Organization 2014. available from http://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf"

In this article (J Korean Med Sci 2015;30:378-384), as Abcertin® does not meet the exact definition of biosimilar, the authors would like to delete the phrases "a biosimilar of imiglucerase" in Page 379 and "a new biosimilar to imiglucerase" in Page 382.

Thank you.

Sincerely yours,
Yoo HW

Results after 24 weeks – no long term data

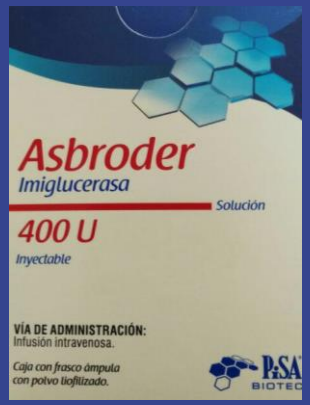
Table 2. Efficacy parameters in a phase 2 study of five patients with Gaucher disease

Parameters	Baseline	24 weeks	Percentage change at 24 weeks	*P* value
Hemoglobin (g/dL)	13.76 ± 1.89	13.86 ± 2.61	0.30 ± 7.63	0.625
Platelets ($\times 10^3$/μL)	154.40 ± 34.62	162.60 ± 47.04	6.86 ± 28.73	1.000
Liver volume (mL)	1,187.0 ± 399.06	1,100.8 ± 380.11	-5.86 ± 16.90	0.438
Spleen volume (mL)	332.0 ± 184.54	330.0 ± 142.26	14.67 ± 69.07	0.625
AST (IU/L)	23.40 ± 4.67	41.60 ± 44.14	68.95 ± 163.63	1.000
ALT (IU/L)	16.80 ± 12.15	38.80 ± 42.48	212.16 ± 446.38	0.313
ACE (U/L)	79.42 ± 31.77	81.50 ± 41.84	-2.59 ± 20.61	1.000
ACP (IU/L)	18.68 ± 8.71	17.10 ± 4.77	-0.92 ± 22.97	1.000
Chitotriosidase (nM/mL/hr)	1,279.82 ± 1,041.47	1,103.76 ± 884.36	-9.11 ± 15.53	0.438
L-spine BMD Z-score	-1.27 ± 0.40	-0.80 ± 0.53	24.56 ± 50.60	0.625
Femur neck BMD Z-score	-0.43 ± 1.37	-0.20 ± 1.35	-147.33 ± 441.79	0.875
Osteosclerosis*	0.0 ± 0.0	0.0 ± 0.0	No change	
Osteonecrosis*	0.2 ± 0.45	0.0 ± 0.0	-100.0	1.000

*None, 0 points; Mild, 1 point; Moderate, 2 points; Severe, 3 points. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACP, acid phosphatase; ACE, angiotensin converting enzyme; BMD, bone mineral density.

Korean Med Sci. 2015 Sep;30(9):1373

- Does not meet regulatory definition of biosimilar
- Was not approved as biosimilar in Korea
- No significant data on purity, safety, efficacy
- No comparative data with imiglucerase
- In Mexico, abcertin give in same bag mixed with imiglucerase – this is dangerous to patients



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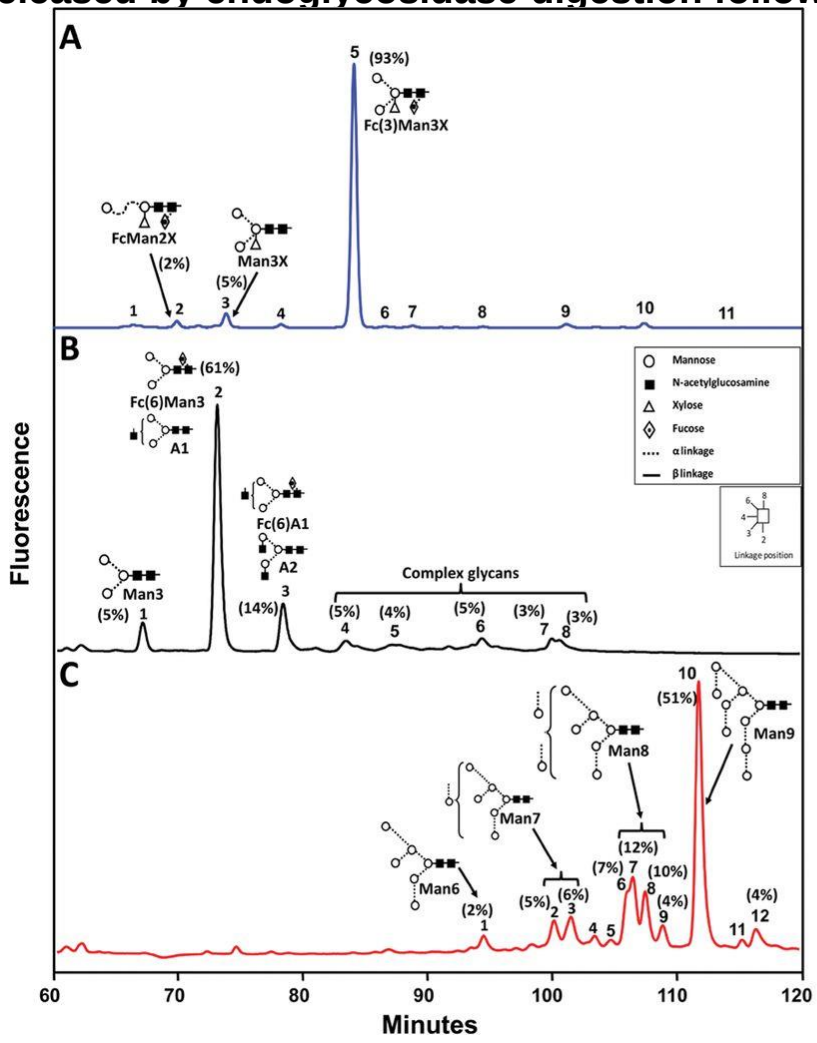
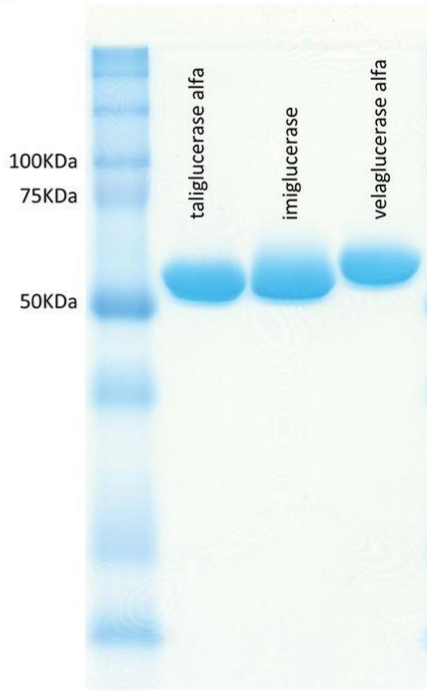
Comparison of the glycosylation profile of IMIGLUCERASE (B), TALIGLUCERASE (A)and VEALGLUCERASE (C) taliglucerase alfa. Representative NP-HPLC separation of glycans released by endoglycosidase digestion followed by fluorescent labelling





Yoram Tekoah et al. Biosci. Rep. 2013;33:e00071

Comparative Therapeutic Effects of Velaglucerase Alfa and Imiglucerase in a Gaucher Disease Mouse Model

You-Hai Xu[1,2], Ying Sun[1,2], Sonya Barnes[1], Gregory A. Grabowski[1,2]*

1 Division of Human Genetics, Cincinnati Children's Hospital Research Foundation, Cincinnati, Ohio, United States of America, **2** Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, United States of America

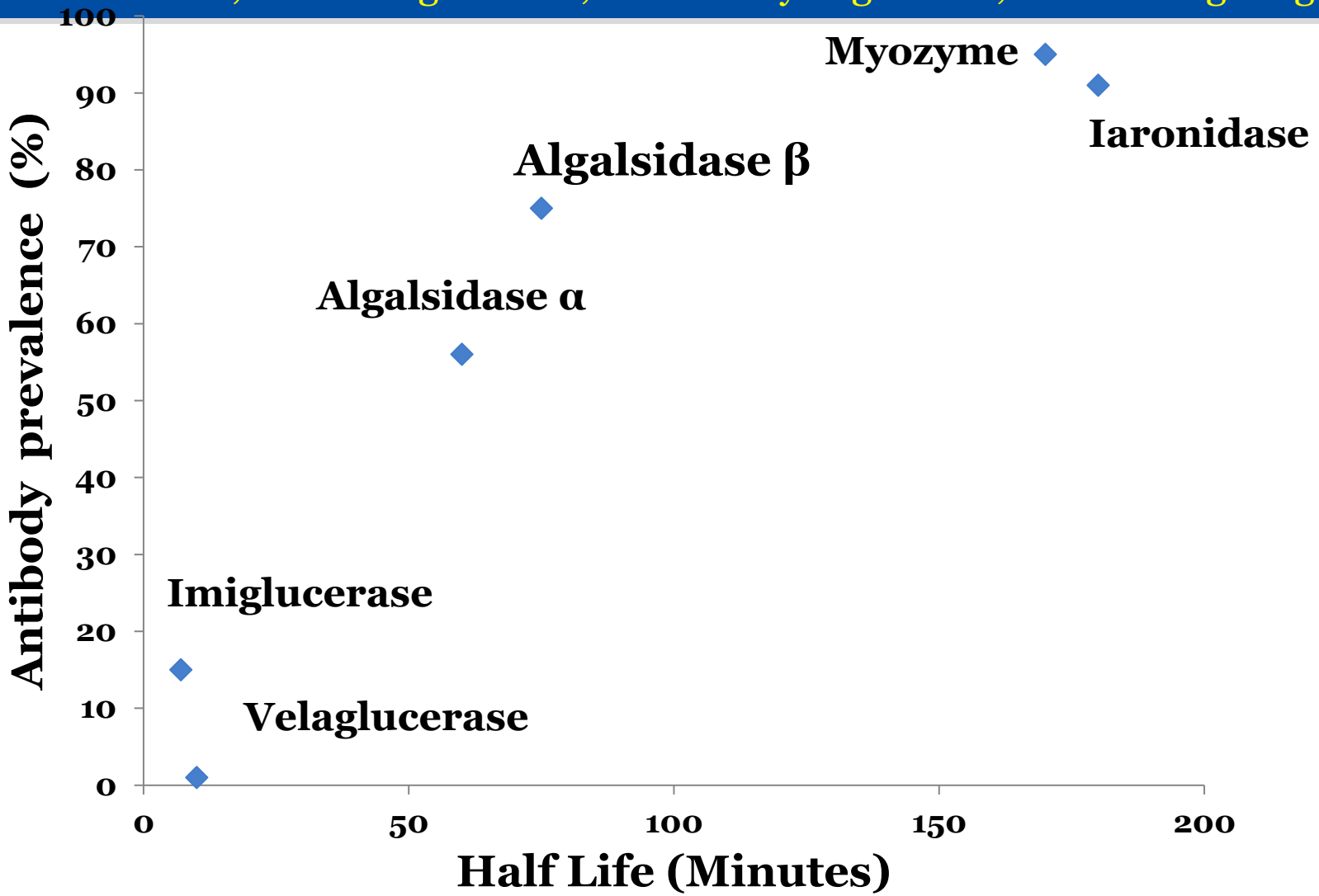
Table 4. Recovery of Vela or Imig activity in serum and organs of 9 V/null mice[A].

Enzyme	Serum[B]		Liver[C]		Spleen[D]		Lung[C]	
	5-wk	20-wk	5-wk	20-wk	5-wk	20-wk	5-wk	20-wk
Imig	65.53±3.31	60.21±1.76	54.36±1.84	71.86±2.52	0.25±0.25	3.40±0.37	0.12±0.01	0.20±0.06
Vela	63.06±4.62	58.16±1.61	57.53±1.35	60.36±2.01	1.86±0.06	2.62±0.08	0.1±0.01	0.04±0.01

[A]The recovery of injected Vela or Imig was calculated as the percentage (% ± SE) of total serum or whole organ activity at the peak of enzyme activity following a bolus of 60 U/kg injection.
[B]The peak activity in serum was 2 min post injection.
[C]The peak activity in liver and lung was 20 min post injection.
[D]The peak activity in spleen was at 40 min in 5-wk mice and 20 min in 20-wk mice post injection.

Antibody Formation in ERTs for LSDs

Determinants:
CRIM status, circulating half life, immune dysregulation, cellular targeting



Desnick RJ and Schuchman EH, Ann Rev Genomics and Human Genetics, 2012

FDA guidance on ADA for biologics

- Patient immune responses to therapeutic protein products have the potential to affect product safety and efficacy.
- The clinical effects of patient immune responses are highly variable, ranging from no effect to harmful effects to patient health.
- Detection and analysis of ADA formation is a helpful tool in understanding potential patient immune responses
- FDA recommends adoption of a risk-based approach to evaluating and mitigating immune responses to or immunologically related adverse clinical events associated with therapeutic protein products that affect their safety and efficacy
- Immune responses may have multiple effects, including neutralizing activity and the ability to induce hypersensitivity 61 responses.
- Immunogenicity tests should be designed to detect ADA that could mediate unwanted biological or physiological consequences.

https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf
Accessed Sept 25, 2017

FDA guidance on ADA to biologics

- FDA cautions that comparison of ADA incidence among products, even for products that share sequence or structural homology, can be misleading. This is because detection of ADA formation is highly dependent on the sensitivity and specificity of the assay.
- Additionally, the observed incidence of ADA (including NAb) positivity in an assay may be influenced by factors such as method, sample handling, timing of sample collection, concomitant medications, and disease condition.

https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf
Accessed Sept 25, 2017

Case presentation

- Female. DOB 09/2008
- Epistaxis since age 2
- Age 5: splenomegaly by PCP on routine exam. Hb 10.7, platelets 94
- Liver biopsy: Gaucher cells
- Genotype N370S/217delC. LV 1.69 x N, SV 10.7 x N, osteopenia
- Started vpriv March 2014 until Sept 2015

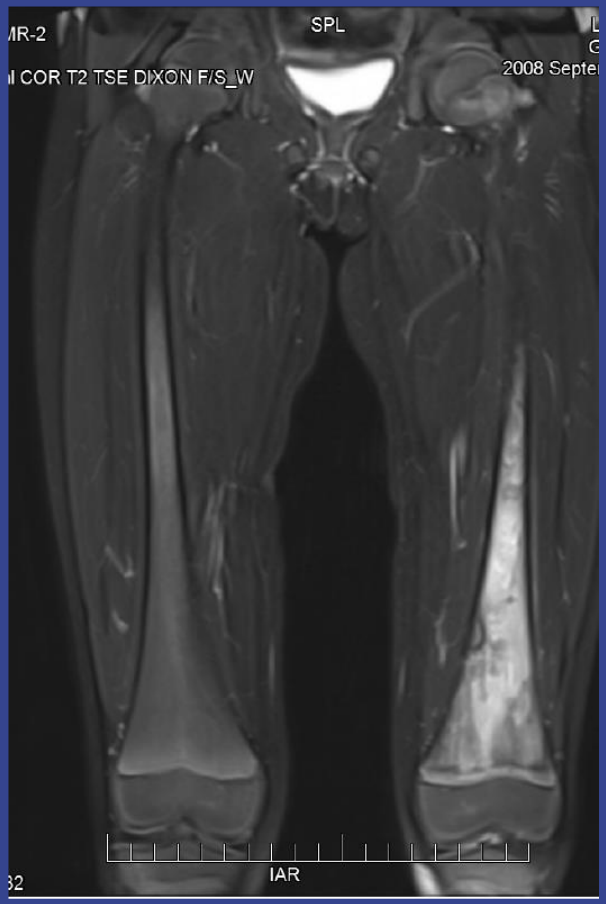
- Falling blood counts and AVN in L femur in Nov 2015
- Changed to taliglcuerase – severe IAR

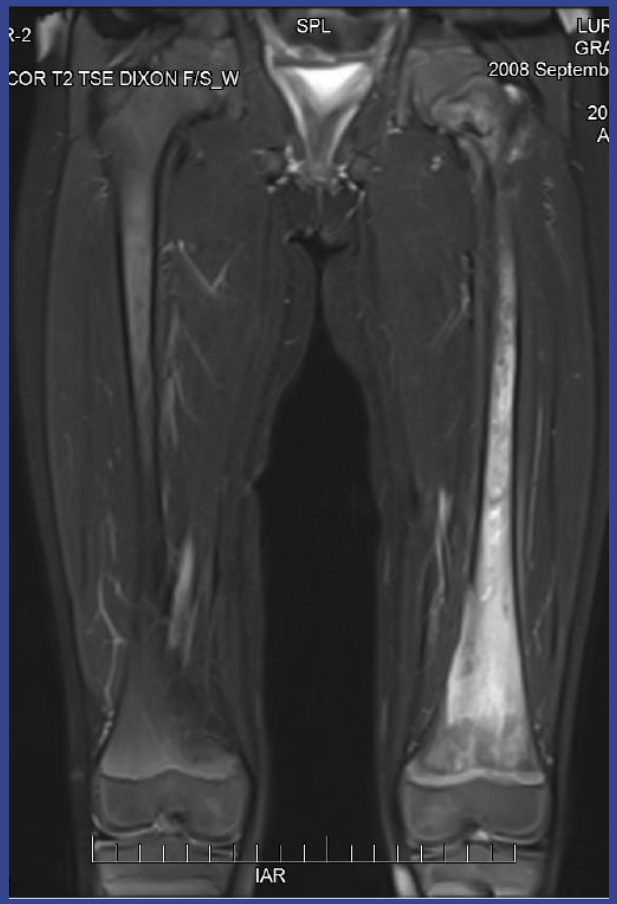
- Seen at Yale Dec 2015: IgG anti-vela antibody titer 163,840, neutralizing antibody titer 160

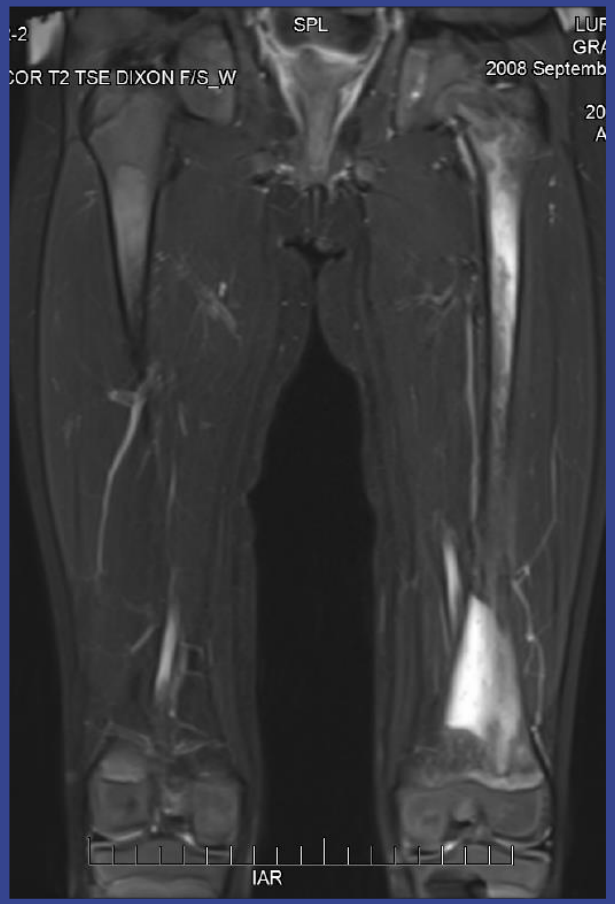
- January 2016 AVN in R femur

- *Affected brother also developed high titre of Neutralizing ADA*

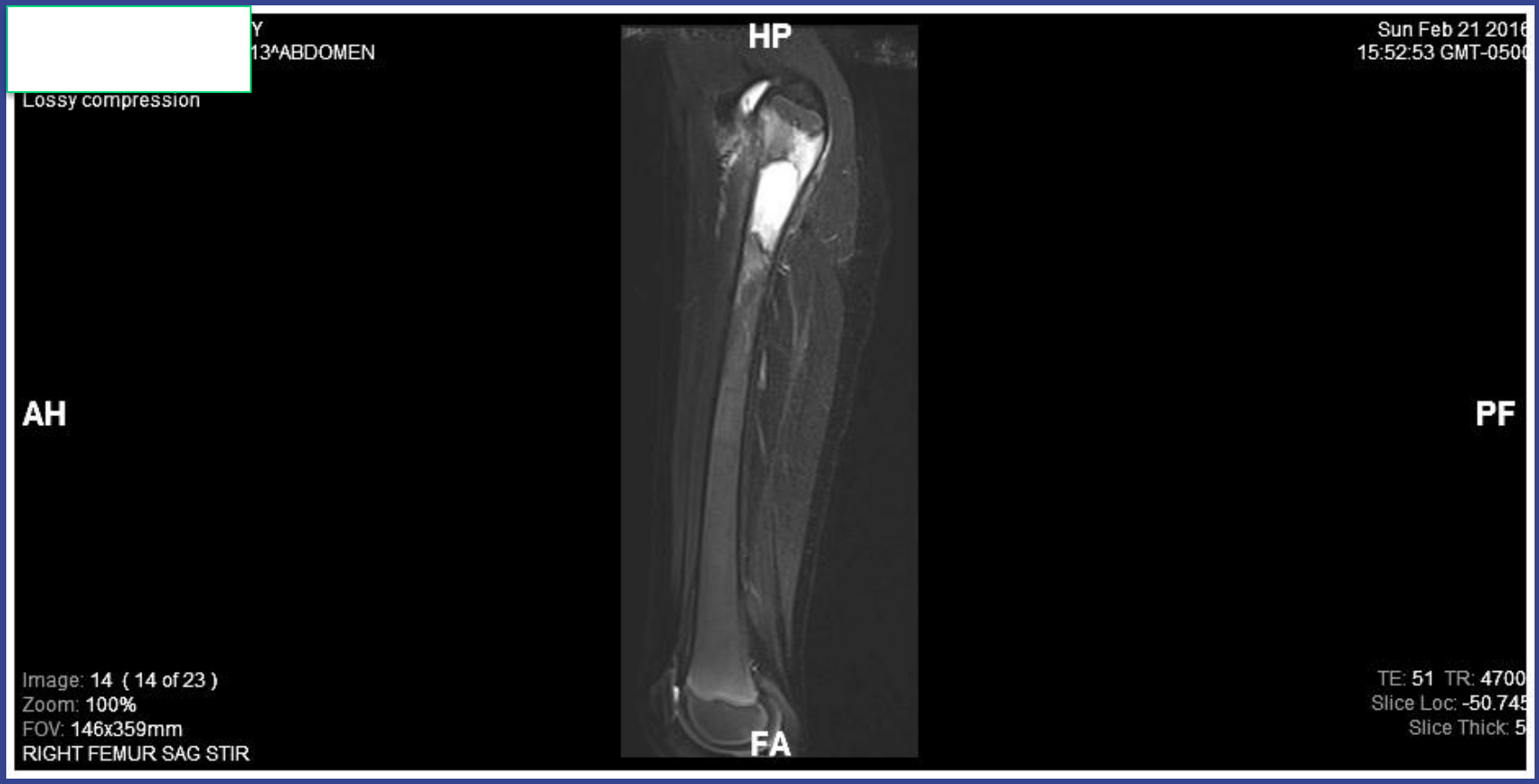
P.K.Mistry, et al manuscript in preparation







December 31, 2015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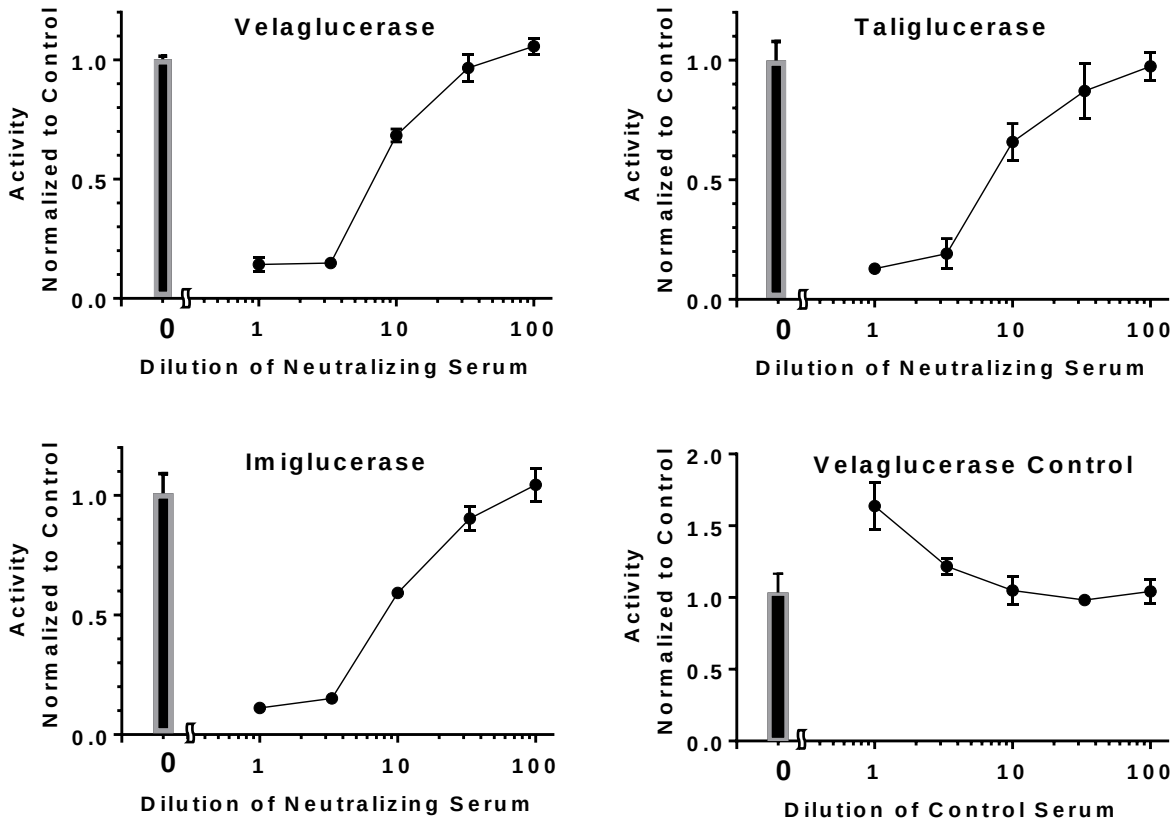
Comparison of antigenicity of three ERT proteins

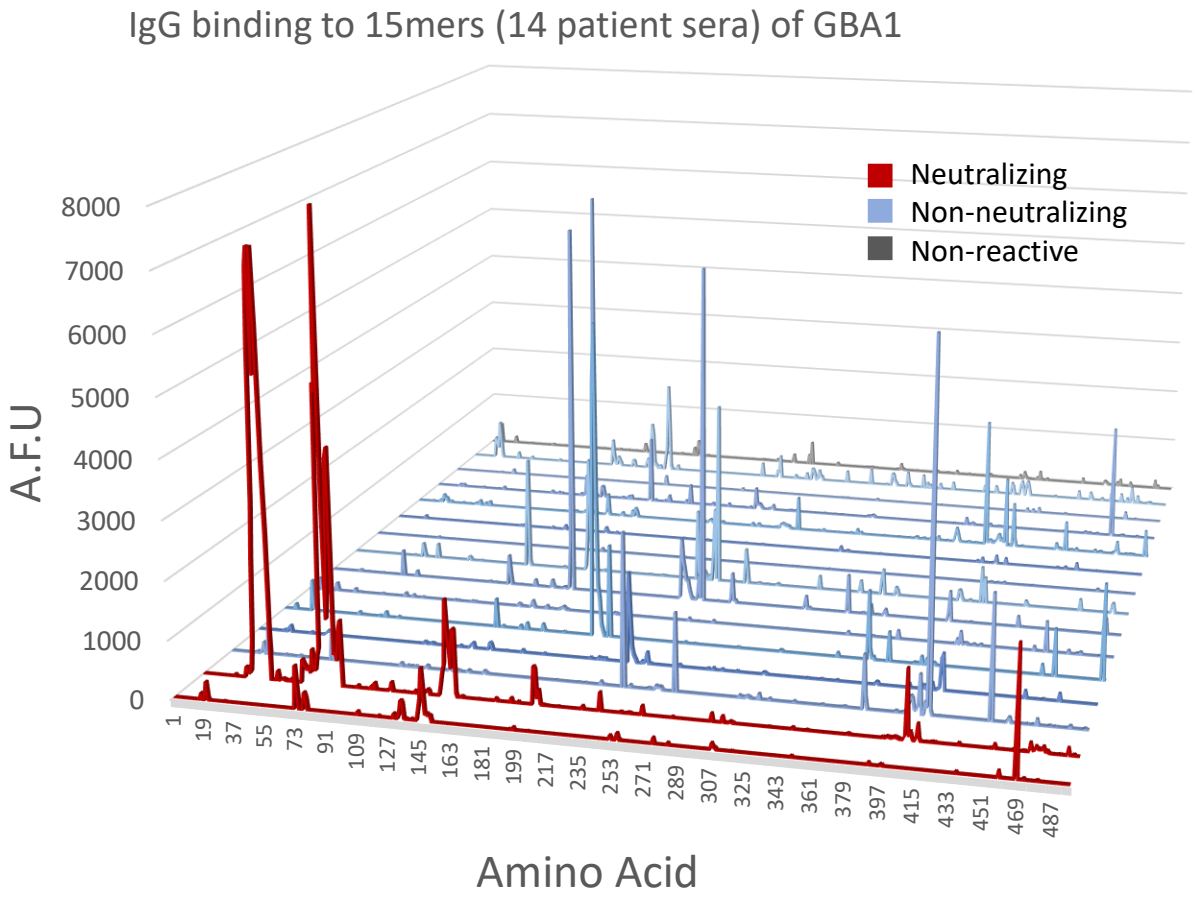


P.K.Mistry, et al manuscript in preparation

Antigenic Hotspots in ERT induced IgG

Epitope Mapping of VPRIV using Patient Sera Containing Neutralizing and Non-neutralizing AB

15 amino acid peptide arrays were probed with patient sera



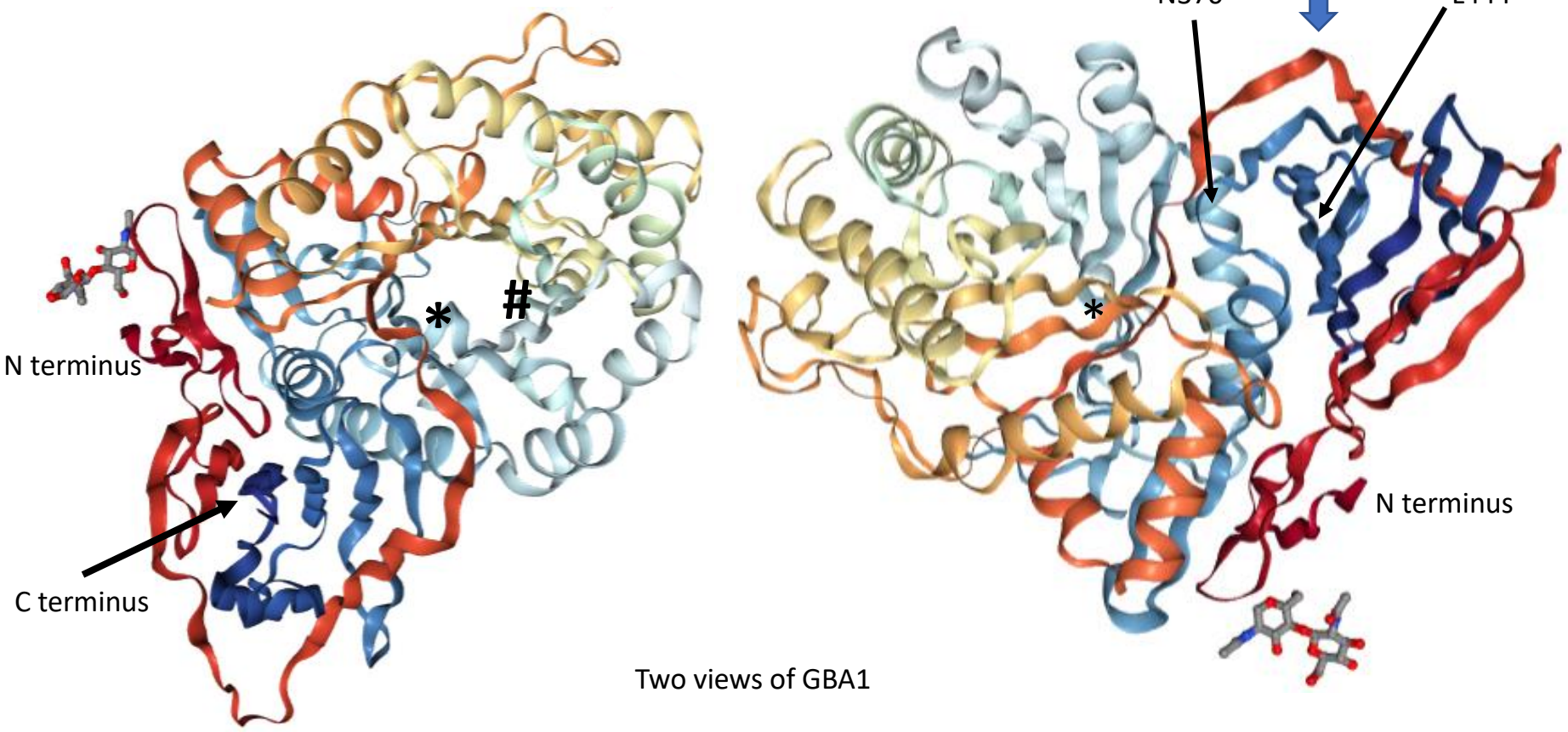
Fig? IgG binding on 15 mer scanning microarrays of Velaglucerase . 1:25 dilution of patient sera was applied to arrays. Red = neutralizing sera, blue= non-neutralizing sera, black = non-reactive sera. Sera producing highest peaks (Arbitrary fluorescence units (AFU)) not drawn to scale.

P.K.Mistry, et al manuscript in preparation

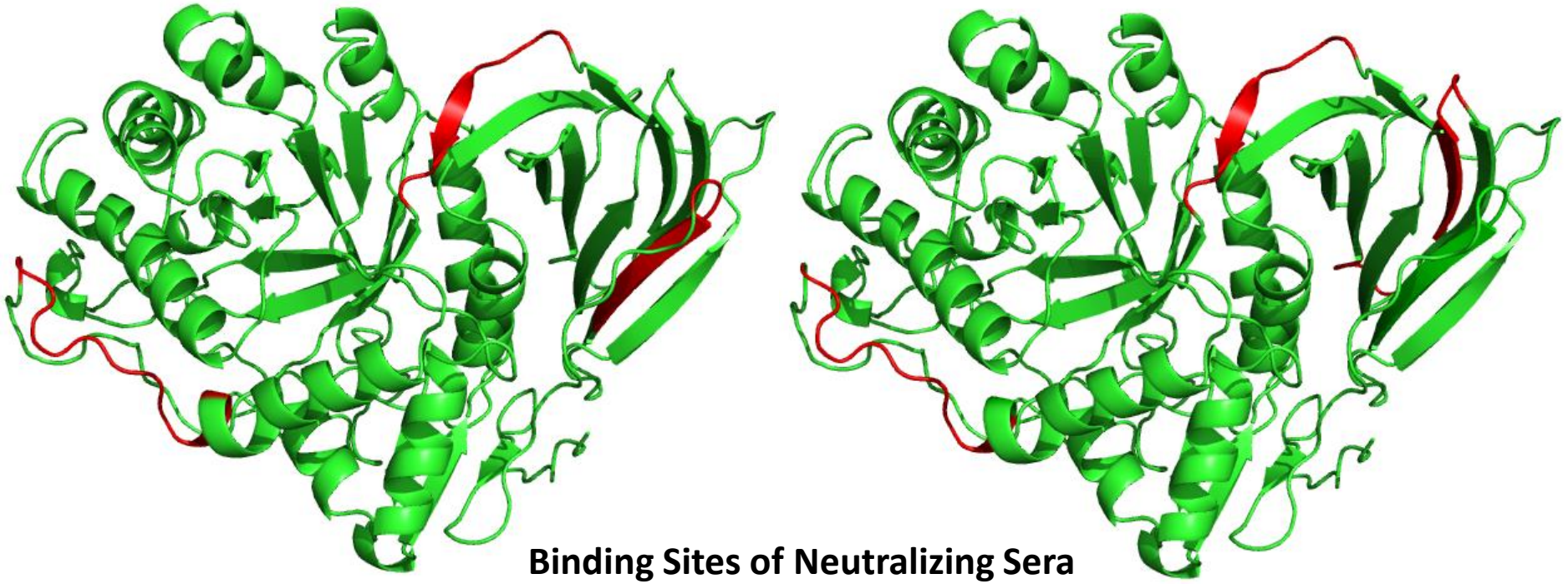
*= E340 active site

#= E235 active site

GBA1



Two views of GBA1

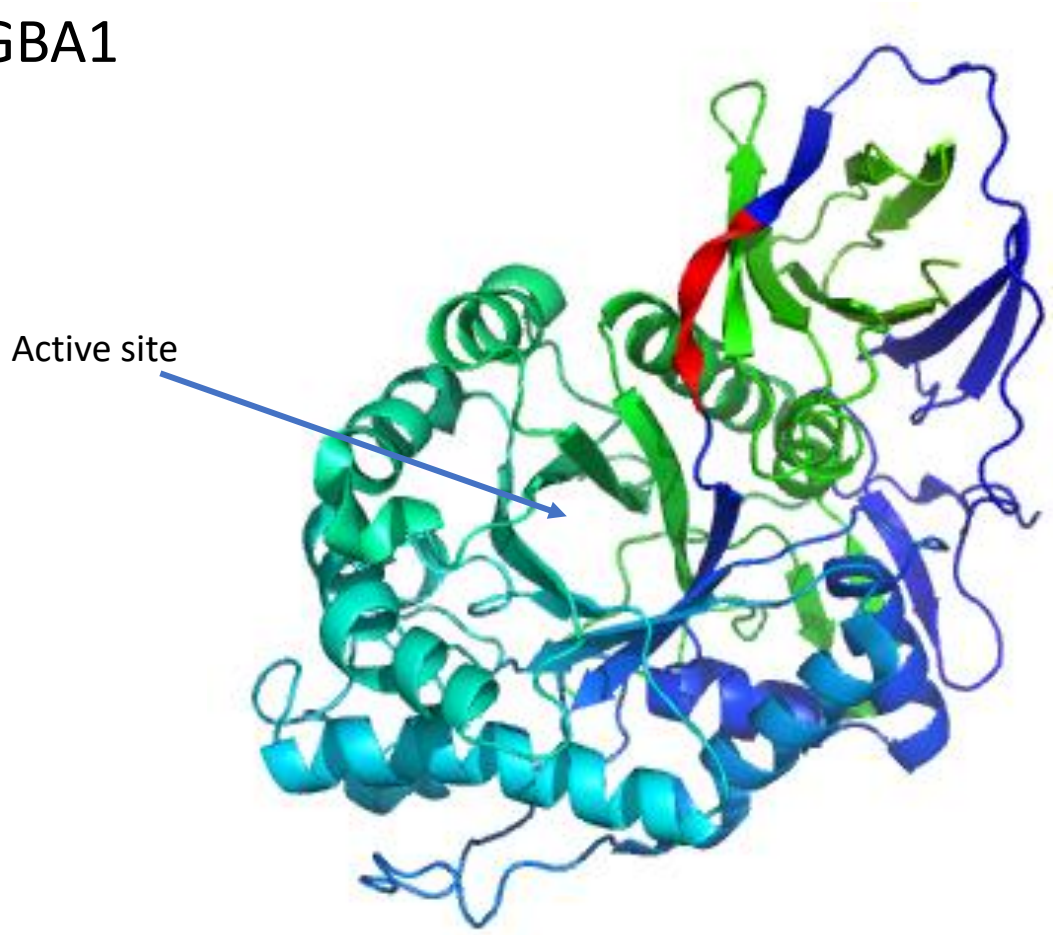


Binding Sites of Neutralizing Sera

Fig? Regions of binding as determined by peptide microarray mapped onto the 3D structure of GBA1 for two siblings with neutralizing AB.

Note: Left is grace right is grant.

GBA1



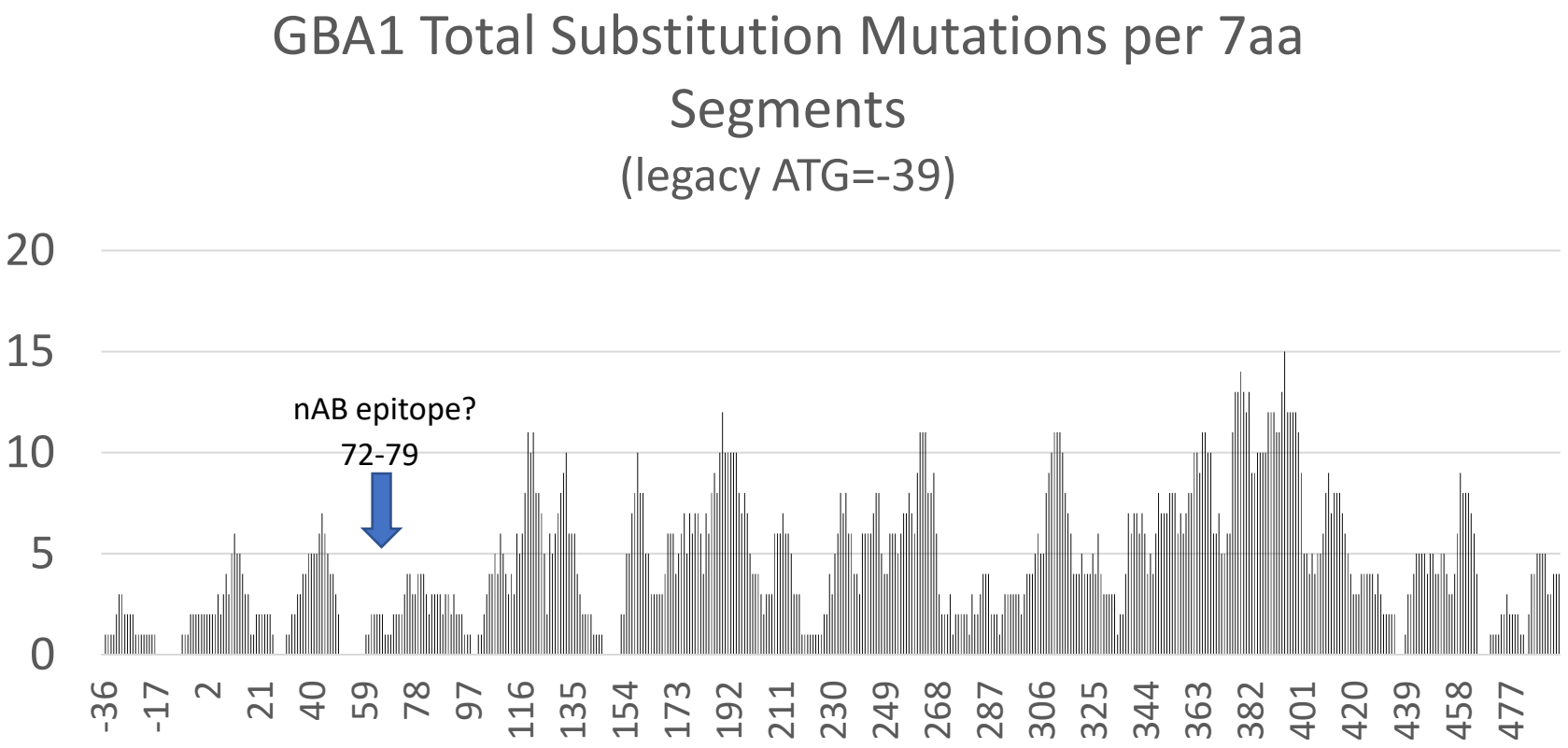
Only the two patients with neutralizing AB have epitope shown in red

EQKFQKVK
aa72-79

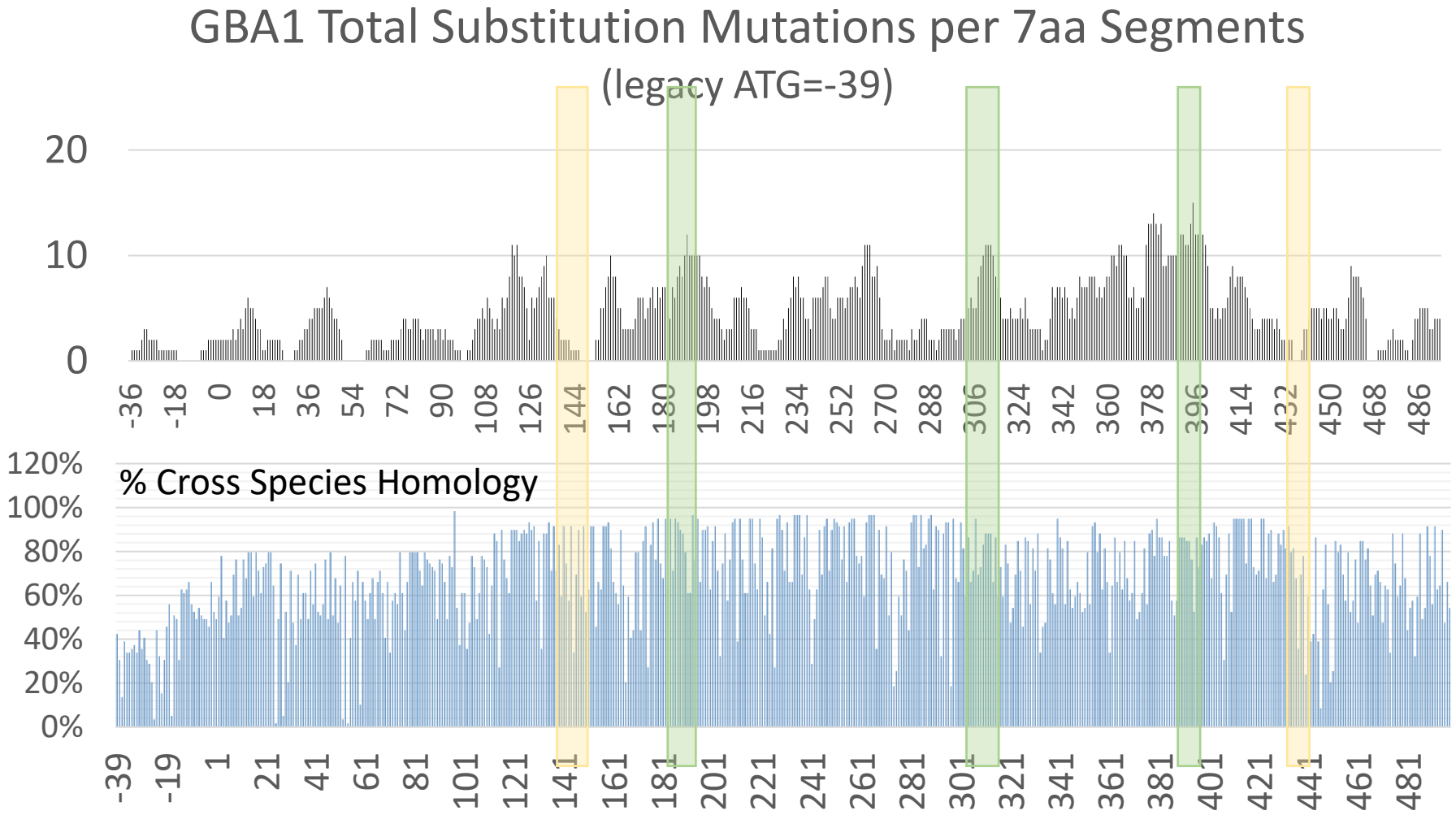
Mutations found near/in putative epitope for neutralizing AB binding (aa72-79)

HGMD codon change	Legacy change ATG=-39	HGVS (nucleotide)	HGVS (protein)	Reported phenotype	Reference
CAG-TAG	Gln73Term	c.334C>T	p.Q112*	Gaucher disease	Beutler (2005) Blood Cells Mol Dis 35, 355 Xiong (2015) Science 347: 1254806 [Additional report]
AAG-TAG	Lys74Term	c.337A>T	p.K113*	Gaucher disease	Grace (1997) J Clin Invest 99, 2530 Xiong (2015) Science 347: 1254806 [Additional report]
GTG-GCG	Val78Ala	c.350T>C	p.V117A	Gaucher disease	Hruska (2008) Hum Mutat 29, 567
AAG-AAC	Lys79Asn	c.354G>C	p.K118N	Gaucher disease	Beutler (1996) Proc Assoc Am Physicians 108, 179 Liou (2006) J Biol Chem 281: 4242 [Functional characterisation]
GGA-AGA	Gly80Arg	c.355G>A	p.G119R	Parkinson disease	Lesage (2011) Hum Mol Genet 20, 202
GGG-GAG	Gly83Glu	c.365G>A	p.G122E	Gaucher disease 2	Jeong (2011) Blood Cells Mol Dis 46, 11
ATG-ACG	Met85Thr	c.371T>C	p.M124T	Gaucher disease	Hruska (2008) Hum Mutat 29, 567 Yoshida (2016) Pediatr Int 58: 946 [Additional report]

Mutations From HGMD May2017 Total 346



Need to plot these hotspots on the 3D model, and need to compare to a plot of % conservation across species


GBA1 Total Substitution Mutations per 7aa Segments
(legacy ATG=-39)
20
10
0
-36 -18 0 18 36 54 72 90 108 126 144 162 180 198 216 234 252 270 288 306 324 342 360 378 396 414 432 450 468 486
% Cross Species Homology
120%
100%
80%
60%
40%
20%
0%
-39 -19 1 21 41 61 81 101 121 141 161 181 201 221 241 261 281 301 321 341 361 381 401 421 441 461 481

Baseline Characteristics

Baseline Characteristics	Factors	Imiglucerase Therapy	Velaglucerase Therapy	P - Value
Total Number of Patients		48	65	
Age in years mean (SD)		48.7 (17.9)	53 (17.4)	0.20
Gender (%)	Male Female	19 (40%) 29 (60%)	31 (48%) 34 (52%)	0.45
Hemoglobin in g/dl Mean (SD)		14 (1.3)	13.7 (1.6)	0.25
Spleen Volume x Normal Median (IQR)		2.3 (1.9, 4.7)	3.8 (1.7, 5.3)	0.33
Splenectomy (%)	Yes	8 (17%)	18 (28%)	0.18
Chitotriosidase in nm/ml/hour Median (IQR)		742.4 (185.6, 1202.7)	516.9 (117.3, 1041.8)	0.13
Genotype	N37S/N370S Other	27 (63%) 16 (37%)	23 (41%) 33 (59%)	0.04

Avascular Necrosis Incidence in Therapy

	Imiglucerase Therapy	Velaglucerase Therapy	Total
Incidence of Avascular Necrosis			
Absent	48	59	107
Present	0	**6***	6
TOTAL	48	65	113

*Percentage of patients with incidence of AVN in population studied = 9.2 %

Fisher's Exact Test: p = 0.038
Chi Squared Test: p = 0.031

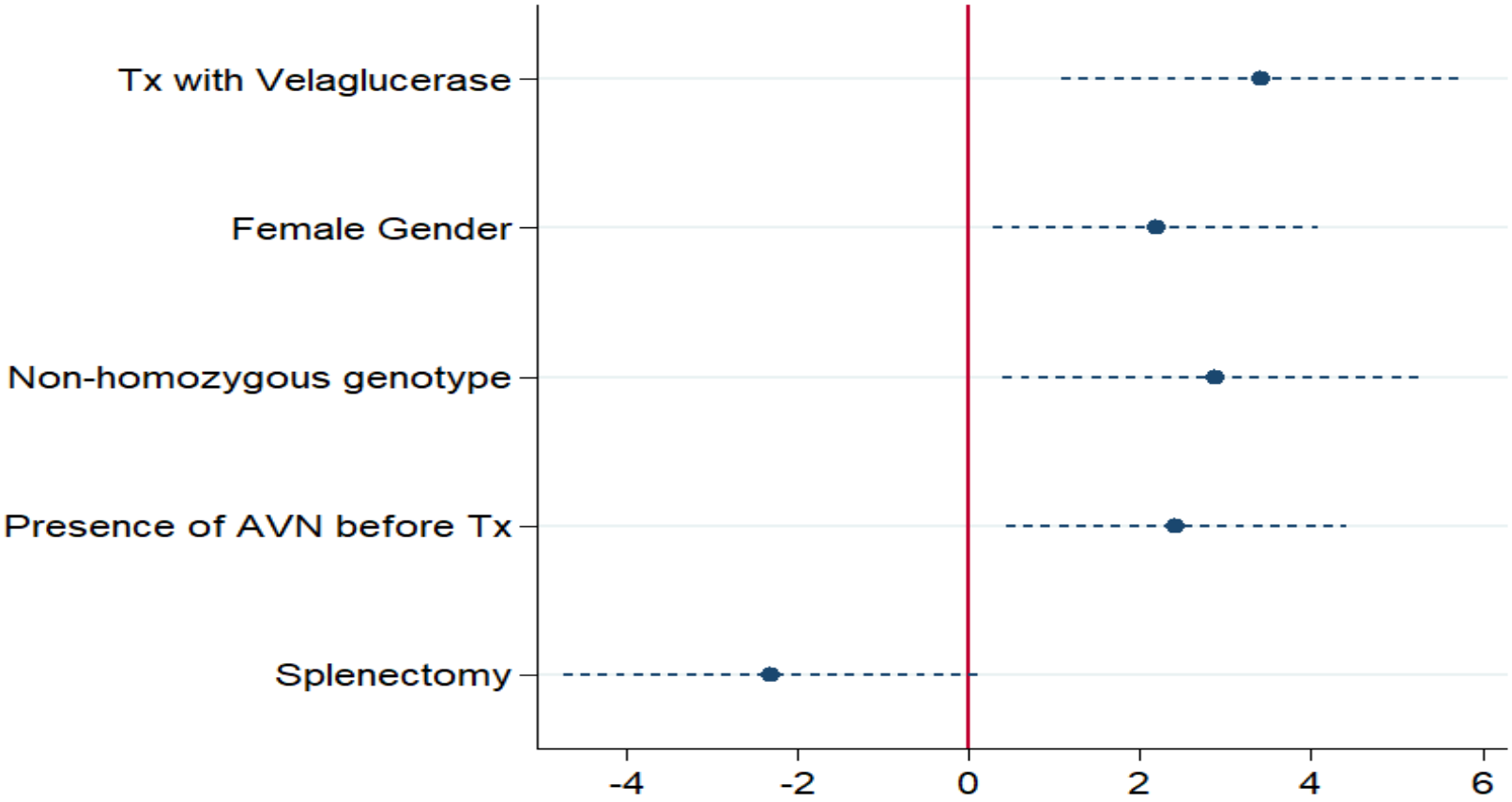
Odds Ratio of Risk Factors for AVN

Logistic regression

Log likelihood = -18.682899

Number of obs	= 121
LR chi2(5)	= 36.36
Prob > chi2	= 0.0000
Pseudo R2	= 0.4932

avn	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Velaglucerase	30.46828	36.30796	2.87	0.004	2.947823	314.9158
Female	8.892631	8.580699	2.26	0.024	1.341797	58.93506
Gender	17.79461	22.46828	2.28	0.023	1.498038	211.3753
Genotype	11.29881	11.45585	2.39	0.017	1.548818	82.42616
AVN before Tx	.0991799	.1223216	-1.87	0.061	.0088432	1.112339
Splenectomy	.0001713	.0003328	-4.46	0.000	3.80e-06	.0077207
Constant						


Tx with Velaglucerase
Female Gender
Non-homozygous genotype
Presence of AVN before Tx
Splenectomy
-4
-2
0
2
4
6

AVN Incidence in Patient-Years

- Velaglucerase 3.54 per 100 patient-years on treatment
- Imiglucerase: 0.09 per 100 patient-years on treatment

Conclusions

- Equivalency of ERTs cannot be extrapolated from visceral/hematolgic response data
- Need for transparent and standardized ADA monitoring
- Interchangeability of ERTs is not recommended
- Long-term data on bone outcomes of newer ERTs is lacking
- Careful evaluation of pan-reactive antibodies is necessary in patients with AE related to ADA before considering switch to another ERT

MAT-CO-2202551 08/2022